An Overnew of the Conference on Low Level Lead Toxicity

by Emil A. Pfitzer*

Alice had come through the looking-glass and had just read an intriguing poem in a book she had found on a table. When she had finished it she said, "Somehow it seems to fill my head with ideas—only I don't exactly know what they are!" On several occasions during this conference, and many times in the past, I have shared Alice's dilemma.

Fortunately for most of us here, this is not our first conference on the toxicity of lead, and it becomes increasingly less difficult to place pertinent ideas and data into perspective. We have really come a very long way in our understanding of low-level lead toxicity. How many conferences, symposia, books, review and research articles have there been since that Public Health Service Conference on Environmental Lead Contamination in December of 1965? Our numbers and efforts have expanded daily and data are being generated almost too rapidly for any one to keep up-to-date with it all.

As stimulating as this has been for the involved and concerned scientist, the past eight years have not been completely joyous ones; rapid expansion can bring its problems. For some it has been the frustration of keeping patience while new investigators rediscover old facts. For some it has been the frustration of watching competitive research dollars being spent for months or years while new investigators learned skills already available in established laboratories. And for some it has been the frustration of feeling that their voices have fallen on deaf ears with no apparent impact on changes in environmental contamination. Despite these frustrations, who can deny that the end results have brought important new techniques and useful new approaches to long-standing problems? Sharp questions have spurred refinement and sophistication of the hypotheses and interpretations. Our intellect and technology have been challenged repeatedly to unearth the data which we must have in order to supply definitive answers.

These advances in knowledge have been taking place concurrently with many other changes. Many of us grew up in a time when the final arbiter about health and disease was the physician. It was simply not respectful to question his judgment about what was good or bad for our health. If any do not realize how far the pendulum has swung away from this tradition, let him speak with those who have recently sought federal funds for human experimentation. I, for one, have accepted the condition that statesmen and legislators will often be the decision makers about factors that influence my health and

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yours. This is not an easy pill for the health scientist to swallow. Our judgments about the risks to health are not always the major determinants for action. One hopes that the decision maker will weigh carefully the facts available from all sources. Our responsibility under such conditions is not only to find the facts about risks to health, but also to communicate these facts in a form which can be used intelligently by the decision makers.

Many of us wear at least two hats in our daily activities—that of the involved scientist and that of the concerned citizen; some of us also wear the hat of the regulatory administrator. Sometimes we are accused of wearing all our hats at the same time and forgetting which is on top. This conference has been remarkably free of such confusion, despite the presence of pending decisions for environmental action which relate to the data which have been presented. So much for general philosophy. What have we learned?

The program has been constructed to focus primarily on two questions: (1) What are the unwanted effects which occur at low levels of exposure to lead? (2) What are the biologically significant major sources of these low levels of lead?

With regard to the first question, we might ask, if we are interested in unwanted effects at low levels of exposure to lead, why we are hearing so many studies with high exposures to lead. There are perhaps several answers to such a question. To some degree it reflects the state of the art for some areas of the problem. In the past I have sometimes accused my fellow scientists of being lesion-hunters. This is a partially "tongue in cheek" accusation, since I've been a lesion-hunter myself. The finding of a lesion is much more easily published for one thing, but the point to be made is that environmental health requires that we demonstrate the absence, not the presence, of a lesion in order to evaluate safety, a far more difficult and time-consuming activity.

Nevertheless the finding of a lesion and an understanding of its pathogenesis is essential, because if we don't know the toxic effects we can't be sure that we have looked in the right place with our most sensitive tools. Thus, typically we need to establish where to look by high-level exposures and then, hopefully, move on to low-level exposures. Sometimes investigators never get around to the low-level exposures.

Following Pentschew's establishment of the fact that lead can cause morphologic lesions in the brain of suckling rodents, other investigators have used that animal model to search for biochemical lesions which may precede the morphologic lesions. Dr. Krigman showed the morphologic details of this lesion with emphasis on myelin formation and neuronal architecture but did not find significant biochemical changes as measured by ganglioside composition. On the other hand, Dr. Michaelson reported that changes in metabolic activity of the brain cells as well as changes in the neurochemical dopamine were found wtih this animal model. Furthermore, studies at somewhat lower levels showed both changes in the neurochemical dopamine and an increased spontaneous motor activity of the rat. While the dietary levels used were still not necessarily low, these findings represent an advance in understanding biochemical changes in the brain following lead exposure.

Dr. Krigman cautioned that the changes in the animal model may not be analogous to lead encephalopathy in children even though other investigators think they might. Dr. Clasen showed the morphologic details of changes in the brain of rhesus monkeys with severe lead encephalopathy as well as in a brain from a lead-exposed baboon obtained from the researchers at New York University. Thus, there are now considerable data on the production of lead encephalopathy in both the rodent and the primate. In addition, evidence has been presented that the rodent, at lower but still high exposure, showed changes in spontaneous motor activity and at least one neurochemical entity. Dr. Silbergeld showed that the mouse also demonstrated hyperactivity and that this activity may be altered by the same drugs used in the treat-

ment and diagnosis of hyperactivity in children, thus, lending further support to the clinical relevance of this animal model. Dr. Cohen showed that the infant baboon provides a very satisfactory animal model, in that not only can lead encephalopathy be produced, but also the sensitive, low-level changes in heme synthesis are more similar to the human than other available nonhuman primates. A progress report was presented of studies designed to quantitate the potential hazards from lead in paint.

Dr. Carson found that lambs from lead-exposed sheep showed slowed learning. The mothers had been exposed to large quantities of metallic lead but the concentration of lead in their blood was only 34 μg-%. The significance of this apparent low-level lead toxicity must certainly be explored further.

It is clear that behavior in humans might be most closely related to behavior in nonhuman primates. Dr. Allen showed that appropriate animal models are now available and that they do respond at varying levels of lead exposure. We can now look forward to attempts to detail the levels of lead exposure which do not produce these changes. We can also look forward to a better understanding of the neurochemical mechanism which may be responsible for some brain dysfunction. It must not be forgotten that the lesions leading to nonspecific behavioral changes may not in any way be associated with lesions related to severe brain dysfunction. But in any event, we have a model which allows a kind of investigation which had not previously been available. We have considerably refined our animal models to look for the unwanted effects of lead in the central nervous system. We must now quantitate the dose–response relationship down to safe levels.

It is fortunate that we do not always need to extrapolate from animals to humans. Animals can provide the opportunity to search for underlying mechanisms, but behavior can be measured in man and children. Our tools may still be crude. Dr. David found evidence that many hyperactive children had higher blood levels of lead than did matched nonhyperactive children. He contemplated the public health significance of this finding and questioned whether or not there was a causal relationship and if so, whether it was reversible. Dr. Pueschel found that one-third of the children with evidence of increased lead exposure had nonspecific central nervous system symptoms and that about one-fourth had impairment on neurologic and motor examination. These changes did not improve over one and one-half years, despite efforts to eliminate excessive lead exposure.

On the other hand, Dr. Albert found that asymptomatic children with high concentrations of lead in teeth did not show significant impairment based on psychological tests and school records. Dr. Alexander also found that children in England differing in the content of lead in blood did not show differences in mental function. Dr. Barocas suggested that our data to date are very crude and he described ways in which behavior may be observed and quantitated so that these questions may be more clearly pursued.

Effects on the blood system were not ignored in this conference. Dr. Angle looked at Na/K ATPase in the red blood cell and suggested that there were slight changes with increase in lead in red blood cells. In contrast with δ-ALA dehydratase, this enzyme may well have significance in the function of the red blood cell. Dr. Rosen took advantage of new sensitive analytical methodology to quantitate lead in plasma. He found a surprisingly stable concentration of lead in plasma over a considerable range of values for lead in whole blood. He also noted the apparent competitive nature of calcium ion with lead for complexing with the red blood cell membrane and suggested roles for calcium and chemicals influencing calcium ion upon the tendency of lead to bind to red blood cells. These observations may provide more insight into the mechanisms for the effects of calcium and iron on lead toxicity as described by Dr. Mahaffey. There appeared to be great interest in her descriptions of the

nutritional influences upon effects of lead in children.

High-level exposures of animals to lead were reported by Dr. Moore and Dr. Gainer. Dr. Moore provided new knowledge about the nature of lead-protein complexes in kidney cells. He identified both an insoluble complex which is the inclusion body and a soluble complex which may have significance in membrane transport. Dr. Gainer showed that lead may interact with other disease states such as viral diseases. Lead had a marked influence on the degree of mortality caused by infection with viruses.

It is clear that our major concern is to establish the nature of unwanted effects and to determine the dose response relationships with particular emphasis at low levels of lead exposure. We are particularly concerned with the differences between the child and the adult as they influence the nature of the dose–response curve. A great deal of our literature on lead toxicity is based on studies with adults, both animals and humans. This conference has presented new information about the effects of lead in the very young animal and in children. Dose–response relationships for this segment of the population are critical for our consideration.

A few general comments of a somewhat theoretical nature about dose–response relationships seem pertinent. In toxicology the foundation of our science has been established on the significance of the dose–response relationship and the belief that for most chemicals a threshold level in the body exists at which animal or man can interact with the foreign chemical resulting in no undesirable effects. Traditionally these studies are performed by exposing animals to various dose levels, then determining the dose level which was not significantly different from the control group and referring to this as the "no-effect" level.

Statisticians have pointed out that when "no-effect" is based on nonsignificance at 95% confidence limits, there remains a 5% probability that there might have been a significant difference between that treated group and the control group. In recognition of this probability of uncertainty, some statisticians, particularly some in federal regulatory agencies, have taken an extremely conservative approach in which the data are not reviewed by actual statistical analysis between individual groups but by the examination of an overall dose–response relationship, with the application of confidence limits to probable slopes for that relationship, then the extrapolation of this statistically possible slope towards the zero dose level of the control group. The acceptable level of exposure is then estimated based upon some very small change which is a presumed "acceptable" fraction of the normal variation within the control group. This approach is not only a very conservative one, it in fact belies the basic belief in a threshold effect. This is pointed out because there is in the mind of some scientists, as well as laymen, the belief that chemicals that produce severe toxic effects at some level must be doing something bad at any lower level and an inherent belief that there may not be a threshold, even for such a chemical as lead.

Whatever our individual beliefs are, there should not be any confusion as to which technique is applied when we examine our data and try to establish quantitative dose–response relationships. If one is confused with the technique for the interpretation of data and does assume what was described as the more conservative approach, most of our experimental research to date does not have large enough groups of animals to reach the definitive decisions utilized for safety evaluation.

The second question of the conference was "What are the biologically significant major sources of low level lead? Biological significance refers to the quantities of lead that are eventually absorbed into the body. A corollary to this question is the one repeated over and over again. "Do children absorb lead at a different rate than adults?"

The presentation by Dr. Wetherill was particularly intriguing. His use of the stable isotope, ^{204}Pb to perform an extremely elegant study represents a major breakthrough in the ability to understand absorption rates

and the modeling for accumulation and retention of metals such as lead. It was comforting to note that his results were in good agreement with the data that have been used in our current models. Hopefully, the availability of this technique can be extended to greater numbers of subjects and also from adults to children.

Dr. Alexander presented data, some of which had been previously published, which again brought forward the very significant finding of major absorption in children, i.e., 53% of ingested lead. Many in the audience expressed concern for this very high rate of absorption and it was pointed out that measurements of fecal lead as a basis for estimating absorption are notoriously variable depending upon the length of time over which one makes observations. Reference to Dr. Kehoe's data shows that there were long periods of time in which the adults were in either negative or positive balance and that the percentage absorption by adults of about 10% was based on average values collected over many months of observation. Nevertheless, Dr. Alexander's data were quite consistent for the eight subjects studied and lead balance studies in children have been needed for a long time.

Dr. Carpenter demonstrated the well recognized fact that lead does cross the placental membrane and showed that the nature of this transport in the rodent can be studied with radioisotopes. He also noted, very appropriately, that the yolk sac placenta of the rodent is considerably different anatomically from that of the primate and human and that extrapolations from these data must be made with caution.

There certainly is no doubt that there are many children in the United States and around the world who do have elevated blood lead levels. Dr. Anderson presented the studies conducted by the federal government in many U.S. cities. These studies are particularly useful, in that a major effort was made to provide reproducibility of data so that this vast quantity of numbers may be compared without analytical questions.

Dr. Sach's studies in Chicago and Dr. Chisolm's studies in Baltimore again proved in great detail the fact that elevated levels of lead in blood may be found to occur in children if one adequately looks for them and, especially, if one looks among children who live in older housing areas. Dr. Needleman's studies in Boston showed elevated levels of lead in tooth dentine not only in children living in deteriorated housing, but also in children living in housing which is good but located near a major processor of lead. Dr. Strehlow's studies in England among children who live in areas having widely different quantities of lead in soil demonstrated no major differences in the apparent absorption of lead by these children. Dr. Goldberg described the hazards in Scotland related to the storage of drinking water in lead cisterns and in areas in which considerable lead piping is used.

A great deal of new information is now available on the presence of lead in the environment. In 1965 there were considerable data about lead in food and lead in various parts of the environment, but these data have been multiplied manyfold by the major efforts underway to identify sources of lead, particularly in our foodstuffs. Dr. Kolbye presented the results of a very extensive market basket survey by the Food and Drug Administration. These data can be interpreted not only for adults but also for children. Particular attention was paid to lead in canned milk, and it was very reassuring to hear that the quantity of lead in canned milk has been on the decline in recent years, presumably due to greater efforts by the canning industry. Dr. Mitchell also presented very extensive data on lead in food, particularly food available to children, and demonstrated that lead can be present in certain foodstuffs in significant quantities. Dr. Knelson reviewed the information available about lead in air and the models that have been utilized to demonstrate the amount of lead that can be absorbed into the body from the lungs. It was of interest to note the similarity between these findings and Dr. Wetherill's data.

Dr. Ter Haar and Dr. Vostal introduced

some new approaches to the estimation of the source of the intake of lead by children. Dr. Ter Haar's work with ^{210}Pb was of particular interest and certainly makes one wonder why this approach had not been utilized years ago. Our associates in the radiological health field have been measuring ^{210}Pb in almost everything for many years, and its recognition as a possible marker of sources of lead is of considerable interest. Certainly these observations will need to be expanded and reviewed and refined for better definition. Data were presented which clearly supported the proposal that the lead ingested by children, who were in the hospital with lead poisoning, had arisen from paint from the house and not from dirt in the yards. Dr. Vostal also presented very interesting data demonstrating that dust in households can certainly move from window sills and floors and walls to the mouth by way of the hands. He interpreted his observations to support the proposal that the source of this dust was primarily from the paint and plaster surfaces in the home.

In conclusion I find that the evidence is very suggestive that the most significant, subtle, and sensitive changes due to low-level exposure to lead may be behavioral disorders in children rather than changes in heme synthesis. The methodologies to establish this relationship in a quantitative manner seem to be within our grasp both for studies in humans and laboratory animals. The preponderance of evidence also identifies lead in paint, plaster, and dust in older housing as the major sources related to current health problems, although substantial efforts are being made to identify and control other sources.

May we all have the opportunity to share again our knowledge about lead in the environment in the very near future, looking forward to significant findings which are on the near horizon. We must all be very much indebted to the sponsoring organizations for this opportunity to work together for the preservation of human health and the world's environment.